REMARKS

Claim Status

Claims 7-19, 21-27 and 29-40 are currently pending.

Priority

In this final Office Action, the Examiner agrees with Applicants that the effective filing date for claims 35, 38 and 39 is the filing date of an earlier application Serial No. 08/514,875, i.e., August 14, 1995. However, the Examiner states that the same '875 application does not teach or describe covalently bound DNA and as such, the effective filing date for claims 14 and 29 is the filing date of a later application Serial No. 08/688,488, i.e., July 30, 1996. In response, Applicants respectfully disagree for the reasons previously presented. Notwithstanding, Applicants herewith accept July 30, 1996 as the effective filing date for claims 14 and 29 of the present application in the interest of furthering the examination.

Rejection under 35 U.S.C. § 102

Claims 7-19, 21-27 and 29-40 maintain rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Fodor et al. (U.S. Pat. No. 6,610,482, "**Fodor**"). Applicants respectfully traverse this rejection.

In maintaining this rejection, the Examiner insists December 6, 1990 be the effective filing date for **Fodor**. Applicants again contend that **Fodor** is not entitled to the benefit of that date when considering the element of "greater than 50 monomers in length" as recited in claims 40 and 56 of **Fodor** for the reasons previously presented in the response of September 14, 2006. Rather, the effective filing date for claims 40 and 56 of **Fodor** should be later than the filing date

of one of **Fodor**'s priority applications, i.e., Serial No. 08/670,118 (subsequently issued as U.S. Pat. No. 5,800,992, "the '992 patent"). That is, the effective filing date for claims 40 and 56 of **Fodor** is later than June 25, 1996.

On page 8 of this final Office Action, the Examiner states that Applicants' previous arguments were directed to disadvantages of construction of an array having all possible probes of a defined length "n" (i.e., complete n-mers) and that any discussion of complete n-mers is not commensurate in scope with the instant claims. Applicants respectfully disagree.

The instant claims are directed to a substrate comprising a microarray having a density of at least 1,000 discrete regions of DNA sequences per cm^2, wherein the DNA sequences are isolated polynucleotides and are at least 50 subunits in length. As claimed, the DNA sequences contained in each discrete region of the microarray can have either the same or different length as long as each of the DNA sequences is at least 50 subunits long. In fact, the instant specification does not exclude the situation wherein the DNA sequences contained in each discrete region of the microarray have the same length. That is, the instant specification does not exclude microarrays of complete n-mers. Contrary to the Examiner's assertion that the instant claims are not drawn to complete n-mer arrays, the instant claims do encompass both an array of complete n-mers with n being at least 50 and an array that contain DNA sequences of different lengths with each sequence being at least 50 subunits long. As such, Applicants' previous arguments are indeed commensurate in scope with the instant claims.

The Examiner points out that the passage cited by Applicants in their previous response does not teach or suggest that probes of 50 nucleotides cannot be synthesized, or synthesis of 50-mers would be disadvantageous. Applicants note the Examiner's statement, however, it is

contended that the disadvantages of synthesizing 50-mers are unambiguously implied by the cited passage as discussed in Applicants' previous response and reiterated below.

The '992 patent discloses that the VLSIPS procedure allows production of ten nucleotide oligomers on a solid phase (*see,* col. 19, lines 36-38) and that the length of oligonucleotides used will be selected on criteria determined to some extent by practical limits (*see* col. 20, lines 62 – col. 21, line 7). The passage goes on:

> For example, if probes are made as oligonucleotides, there will be 65,536 possible eight nucleotide sequences. If a nine subunit oligonucleotide is selected, there are 262,144 possible permeations of sequences. If a ten-mer oligonucleotide is selected, there are 1,048,576 possible permeations of sequences. As the number gets larger, the required number of positionally defined subunits necessary to saturate the possibilities also increases. With respect to hybridization conditions, the length of the matching necessary to confer stability of the conditions selected can be compensated for.

Col. 22, lines 6-12 of the '992 patent further describes the following limitations of the VLSIPS technology in sequencing:

> As the length of the oligomer increases the number of different probes which must be synthesized also increases at a rate of a factor of 4 for every additional nucleotide. Eventually the size of the matrix and the limitations in the resolution of regions in the matrix will reach the point where an increase in number of probes becomes disadvantageous.

The above descriptions of the '992 patent indicate that if a 50-mer oligonucleotide were selected, there would be $1{,}048{,}576^5$ possible permeation sequences. Such an astronomic number of probes that must be synthesized on a matrix would certainly exceed the size and resolution limits of the matrix provided by the '992 patent. Clearly, the above descriptions of the '992 patent undoubtfully suggest that synthesis of 50-mers using the VLSIPS procedure would be disadvantageous, if not impossible.

Further in maintaining this rejection, the Examiner states that Applicants have not provided any factual evidence that **Fodor** could not have produced a microarray of polynucleotides each having more than 50 monomeric units at the effective filing date of the '992 patent (i.e., June 25, 1996). Applicants contend that the allegedly missing factual evidence actually comes from the teaching of the '992 patent itself as discussed above and further explained below.

The above cited passages of the '992 patent, if not explicitly, clearly imply that the VLSIPS technology would encounter tremendous difficulties in producing a microarray of polynucleotides each having more than 50 monomeric units. In fact, based on the teachings of the '992 patent, one (including Fodor's group themselves), at the time of the filing of the '992 patent, would not be encouraged to even try to produce a microarray of 50-mer probes because of increasing disadvantages and difficulties that go along with producing a microarray of increasing length of the oligomers using the VLSIPS procedure. In fact, the '992 patent does not disclose anywhere explicitly or unambiguously that a miroarray of 50-mers is actually produced using the VLSIPS procedure. This is also apparent from the level of "achieved microarrays" in the '992 patent as indicated in Col. 66, line 65 thru Col. 67, line 9: what was actually achieved is the synthesis on glass of eight trimers of C and T. This is clearly not at the level of the microarray of claims 7, 34 and 36 of the instant invention.

Applicants respectfully disagree with the Examiner's allegation that the '992 patent teaches arrays of 50-mer probes in Col. 20, lines 27-39 and Col. 28, lines 40-43. It is contended that the former passage of the '992 patent cited by the Examiner describes the overall size and density of the matrix and has nothing to do with the lengths of probes contained in the matrix.

The latter passage of the '992 patent cited by the Examiner describes the hybridization conditions used in fingerprinting embodiments. In particular, the '992 patent describes:

> Under appropriate hybridization conditions, e.g., typically higher salt and lower temperature, the probes will hybridize irrespective of imperfect complementarity. In fact, -with probes of greater than, e.g., about fifty nucleotides, the difference in stability of different sized probes will be relatively minor. (Col. 28, lines 37-43)

The above passage discusses the hybridization conditions when using a microarray of probes, e.g. in the context of Southern Hybridization. A situation "with probes" of fifty nucleotides and "different sized probes" is outlined. This outlined situation relates to the stability of different sized probes and not to an achieved microarray of 50-mer probes. As such, the above passage of the '992 patent does not provide a microarray of 50-mer probes.

The Examiner further notes that in addition to the VLSIPS technology, the '992 patent also teaches attaching preformed probes onto the array surface. Although it teaches that isolated probe may be attached to the matrix, the '992 patent does not actually teach or suggest that the probes are at least 50 subunits in length. In addition, the same passage cited by the Examiner describes "[t]hese probe reagents may be attached by an automated process making use of the caged biotin methodology described in Ser. No. 07/612,671" (emphasis added). With the term "may be", the '992 patent indicates that the attachment of isolated probes to the matrix at defined positions by using the caged biotin methodology has not actually been achieved at the time of its filing. The caged biotin technology is described in Ser. No. 07/612,671 for the immobilization of anti-ligands such as oligonucleotides. Even if the attachment of isolated probes to the matrix using the caged biotin methodology were achieved, Ser. No. 07/612,671 does not provide a microarray with an achieved density of at least 1,000 discrete regions of polynucleotides per cm^2,

or an achieved microarray of polynucleotides with a length of at least 50 subunits for each polynucleotide.

Overall, the '992 patent does not teach or suggest producing an array comprising polymers having greater than 50 monomers in length, wherein the polymers are synthesized via the VLSIPS procedure or preformed and individually isolated. As such, Applicants contend that **Fodor** should not have been entitled the priority of the '992 patent at least when considering the element of "greater than 50 monomers in length" as recited in claims 40 and 56 of **Fodor**. The effective filing date for claims 40 and 56 of **Fodor** should be later than the filing date of the '992 patent, that is, later than June 25, 1996. Whereas, instant claims 7, 34 and 36 are entitled to at least the filing date of an earlier application Serial No. 08/477,809, that is, June 7, 1995, when considering the element of "at least 50 subunits". It is again noted that the element of "at least 50 subunits" is at least supported by 08/477,809, wherein the specification describes "(e)ach distinct biopolymer (i) is disposed at a separate, defined position in said array, (ii) has a length of at least 50 subunits" (*see*, page 7, lines 26-28), "the biopolymers are polynucleotides having lengths of at least about 50 bp" (*see*, page 26, lines 21-23), and "the polynucleotides have lengths of at least about 50 bp" (*see*, page 29, lines 5-6).

Since claims 7, 34 and 36 of the present application are at least entitled to the priority date of June 7, 1995, which date is well before the priority date for claims 40 and 56 of **Fodor** as discussed above (i.e., later than June 25, 1996), **Fodor** is not a valid prior art reference for claims 7, 34 and 36 of the present application as well as the dependent claims thereof. Consequently, the rejection of claims 7-19, 21-27 and 29-40 under 35 U.S.C §102(e) as allegedly being anticipated by **Fodor** should be withdrawn.

Claims 7-15, 17-19, 21-27, 29-35 and 38-40 maintain rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Winkler et al. (U.S. Pat. No. 6,677,195, "**Winkler**"). Applicants respectfully traverse this rejection.

As presented previously and reiterated herein, **Winkler** discloses a method and device for forming large arrays of polymers on a substrate. In particular, **Winkler** discloses a process of monomer-by-monomer synthesis of polymers to provide a plurality of polymer sequences on a single substrate, wherein the deposition of monomers is carried out by using a deposition device to effect the formation of a polymer in a pre-defined region. That is, the arrays of polymers are formed through an in situ process. Although it mentions that the process "may be" adapted to form polymers having, e.g. 50 monomers or more (*see*, col. 17, lines 53-57, emphasis added), **Winkler** does not actually provide a microarray with each distinct polynucleotide being at least 50 subunits in length. Such "may be" disclosure of **Winkler**'s would not allow an explicit and unambiguous disclosure of a miccroarray which would correspond to the microarray of claims 7, 34 and 36 of the present application. Furthermore, the level of "achieved microarrays" in **Winkler** would appear to be not at the level of the microarray of the present application as **Winkler** illustrates the power of his technique through the synthesis of the complete array of six hexamer peptides from a 20 amino acid basis set (*see*, Col. 11, lines 20-48.)

Furthermore, Applicants previously argued and again emphasize herein that **Winkler** provides no enabling data that arrays of "polymers having 3, 4, 5, 6, 10, 15, 20, 30, 40, 50, 75, 100 or more monomers" could actually be produced using their monomer-by-monomer synthesis process. In fact, the state of the art at the time of the filing of **Winkler** (i.e., Nov. 1992) suggests that no microarrays of polynucleotides with a length of at least 50 subunits were actually produced as evidenced below.

Applicants again submit that **Winkler** and the above-discussed '992 patent share a common inventor (i.e., Stephen P.A. Fodor) and that **Winkler** predated the effective filing date of the'992 patent (i.e., June 25, 1996). As recognized in the '992 patent, which apparently describes the later work of Fodor's group, in situ synthesis has such limitations in sequencing that producing a 50-mer oligonucleotide would seem to be impossible due to astronomic number of probes that must be synthesized on a then-available matrix. The factual evidence which is alleged missing by the Examiner actually comes from the teaching of the '992 patent itself as well as the teaching of **Winkler** as discussed above.

Taking into consideration the state of the art at the time of its filing as well as the fact that it does not actually provide "an achieved microarray" with each distinct polynucleotide being at least 50 subunits in length, **Winkler** could not anticipate the present invention as claimed. Therefore, the rejection of the instant claims under 35 U.S.C §102(e) as allegedly being anticipated by **Winkler** should be withdrawn.

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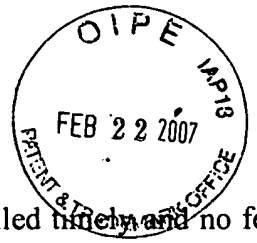

This paper is filed timely and no fees are believed to be due. However, should any fees be required for any reason relating to this document, the Commissioner is authorized to deduct such fees from Howrey LLP Deposit Account No. 08-3038/12665.0009.CNUS01.

Respectfully submitted,

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